No. 11

RESEARCHES ON MORPHINE

PART I.

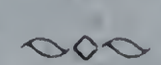
BY

S. B. SCHRYVER, D.Sc., Ph.D.

AND

FREDERIC H. LEES.

[From the Transactions of the Chemical Society, 1900]



The Wellcome Chemical Research Laboratories

Frederick B. Power, Ph.D., *Director*

6, King Street, Snow Hill

London, E.C.

XCI.—*Researches on Morphine. Part I.*

By S. B. Schryver and Frederic H. Lees.

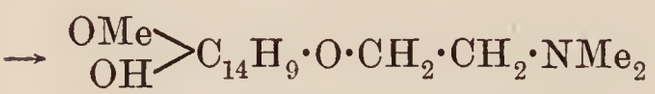
Morphine is a subject of considerable interest from a twofold standpoint, namely, the chemical and the pharmacological. Our knowledge of the subject from the chemical side is due mainly to L. Knorr and Vongerichten.

Older researches have shown that morphine is a phenanthrene derivative, and contains two hydroxyl groups, one of a phenolic character, the other alcoholic. On treatment with methyl iodide (two molecular proportions) in the presence of sodium ethoxide, it yields the methiodide of its methyl ether (codeine), and the hydroxide, derived from this compound, codeine methohydroxide, $C_{17}H_{18}O_2N\cdot OMe,CH_3OH$, on warming with alkalis loses the elements of water, and is converted into methocodeine or methylmorphimethine, $C_{17}H_{17}O_2N(OMe)\cdot CH_3$. This substance is a tertiary base, and on heating with acetic anhydride is converted into the acetyl derivative of dimethyloxethylamine, $OH\cdot CH_2\cdot CH_2\cdot NMe_2$, and the acetyl derivative of a hydroxymethoxyphenanthrene, $OH\cdot C_{14}H_8\cdot OMe$. An isomeric product, β-methylmorphimethine, is produced at the same time. The production of acetyl dimethlyoxethylamine in this way is characteristic of derivatives of the closed ring compound, *N*-methylmorpholine,

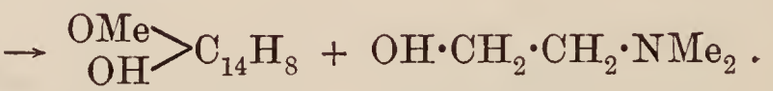
$$\begin{matrix} CH_2\cdot O & \text{——} & CH_2 \\ | & & | \\ CH_2\cdot NMe\cdot CH_2 & & \end{matrix}.$$

Knorr represents the reactions by the following formulæ:

Codeine. Codeine methohydroxide.

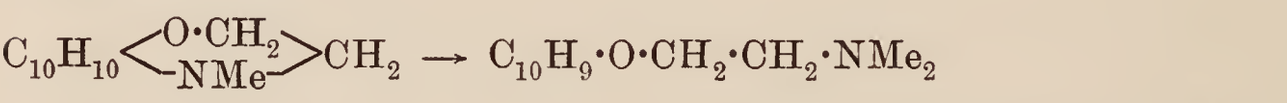


Methylmorphimethine.



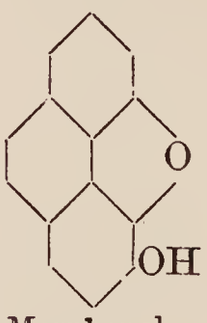
Hydroxymethoxyphenanthrene. Dimethyloxethylamine.

The synthetical base, naphthalanmorpholine, undergoes similar transformations:

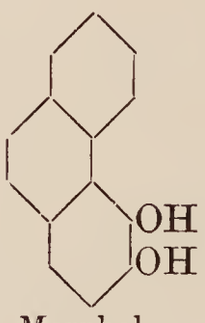


(*Ber.*, 1889, **22**, 181, 1113, 2081; 1894, **27**, 1149; 1899, **32**, 737, 742; *Annalen*, 1898, **301**, 1; 1899, **307**, 171).

Vongerichten's more recent researches deal principally with the nitrogen-free decomposition products of morphine (*Ber.*, 1897, **30**, 355, 2441; 1898, **31**, 51, 3198; 1899, **32**, 1521, 2379; 1900, **33**, 352). He shows that the β-methylmorphimethine discovered by Knorr (*Ber.*, 1894, **27**, 1149) is not acted on by acetic anhydride, but that its methiodide on treatment with alkalis readily decomposes, giving as a main product a monohydroxyphenol, $C_{14}H_8O_2$ (morphenol), which readily reduces to the dihydroxyphenanthrene (morphol), of which the methyl ether was obtained by Knorr, as just described. As a result of his researches, Vongerichten assigns the two following formulæ to morphenol and morphol respectively:



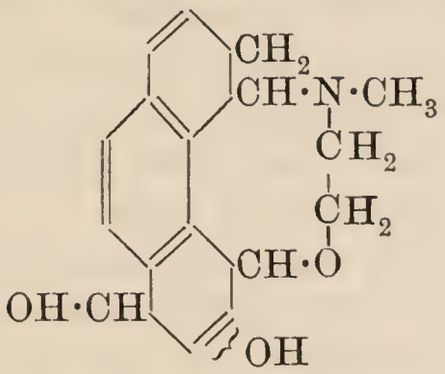
Morphenol.



Morphol.

These formulæ become of special interest in view of the recent researches of Pschorr and his collaborators on the synthesis of the hydroxyphenanthrenes, and from the results we can obtain some clue to the positions which the hydroxyl groups and the morpholine residue

occupy in the phenanthrene nucleus. Knorr and Vongerichten both assign to morphine the following probable constitution :



There still remains to be determined, however, the exact points to which the various hydroxyls remain attached, as well as the relationship existing between the α-morphimethine and β-morphimethine derivatives. By substituting the alcoholic hydroxyl by halogen or other groups or elements, and subjecting these products to the action of various reagents, it was expected that a new series of phenanthrene products might be obtained, which would further elucidate the constitution of morphine.

The second point of interest was to determine the influence of such substitutions on the physiological character of the morphine. Owing to the fact that the methyl ether of morphine (codeine), which occurs amongst the opium alkaloids, has long been employed in medicine, this aspect of the research seemed to be of some practical importance. The investigations hitherto undertaken with the view of determining the influence of substitution on the physiological action of morphine have been confined almost entirely to the preparation of the alkyl and acyl derivatives formed by the substitution of the hydrogen of the hydroxyl groups by various radicles (Stockman and Dott, *Brit. Med. Journ.*, 1890, ii, 189 ; von Mering, *Merck's Annual Report*, 1898, pub. March, 1899 ; Dreser, *Pflüger's Archiv*, 1898, **72**, 485). The compounds investigated have all a modified narcotic action, and as the result of these researches various products have been placed on the market, such as "dionin" (ethylmorphine hydrochloride) ; "heroin" (diacetylmorphine hydrochloride) ; "peronin" (monobenzylmorphine hydrochloride). Furthermore, apomorphine, $C_{17}H_{17}O_2N$, discovered many years ago by Matthiessen and Wright, has an emetic action, and is not usually employed as a narcotic ; its chemical relationship to morphine, from which it is prepared by the action of hydrochloric acid, and from which it differs so considerably in physiological action, remains yet to be determined.

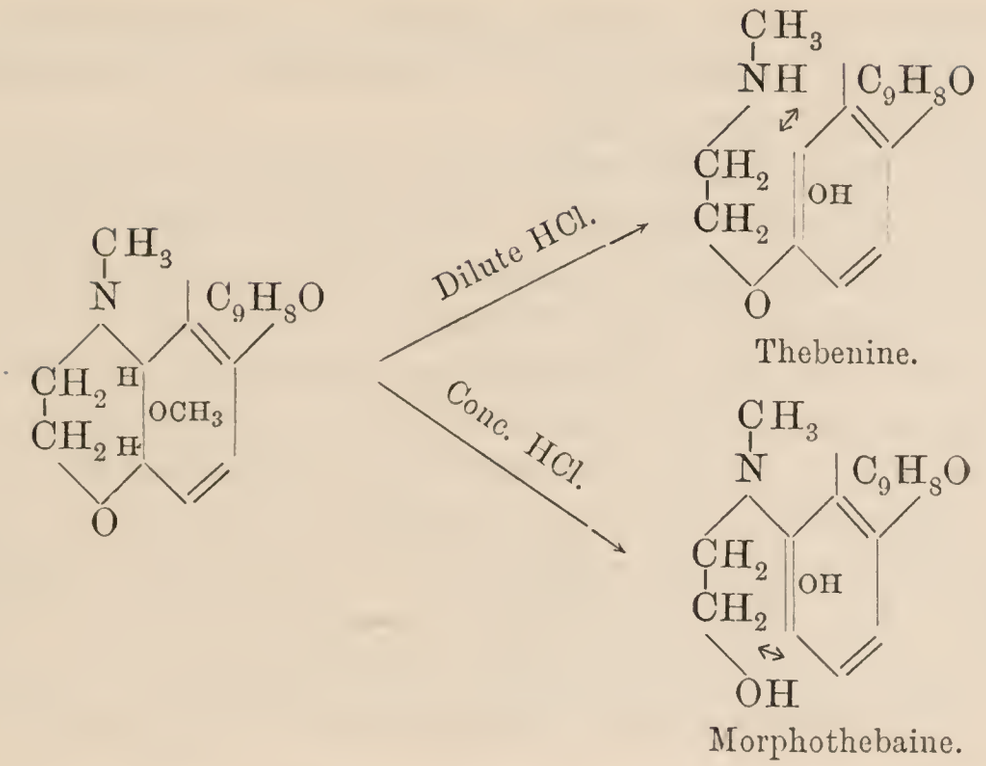
When morphine is treated with phosphorus trichloride, it yields a crystalline base, $C_{17}H_{18}O_2NCl$, in which, as it yields only a monoacetyl derivative, the hydroxyl is replaced by chlorine. This product

is designated *chloromorphide*. In a similar way, by treating morphine with phosphorus tribromide, a *bromomorphide* is obtained. On treating chloromorphide with tin and hydrochloric acid, the chlorine is replaced by hydrogen, and the hydrochloride of a base, $C_{17}H_{19}O_2N$, is formed, which is called *deoxymorphine* in this paper. *None of these products has a narcotic action, even when given in grain doses*, the usual dose for morphine being about $\frac{1}{8}$ grain.

This result seemed at first sight astonishing in view of the fact that the simple synthetical base naphthalanmorpholine, of which the formula is given above, has almost the same physiological action as morphine (Leubuscher, *Annalen*, 1899, 307, 172). On further investigating the halogen products, it was found that this non-narcotic action may be assigned to purely chemical causes. On warming a neutral solution of chloromorphide hydrochloride on the water-bath, it rapidly becomes strongly acid. The free bases furthermore, on heating with water, rapidly decompose and go into solution, giving in the case of bromomorphide the hydrobromide of a base, according to the following equation:

$$C_{17}H_{18}O_2NBr + H_2O = C_{17}H_{19}O_3N,HBr.$$

The product, however, is not morphine, but a crystalline, isomeric, non-narcotic base which we have called *isomorphine*. Several of its salts and derivatives have been prepared and contrasted with those of morphine. Like morphine, it is lævorotatory, but more strongly so, and the salts are very much more readily soluble in water. On treatment with phosphorus trichloride, it yields a product, which has not yet been fully investigated, but which is certainly not chloromorphide. Unlike morphine, it does not reduce gold chloride readily, and as it is the only product produced when bromomorphide is treated with water, and like morphine is lævorotatory, it is highly improbable that it is merely a stereoisomeride. The problem now remains to determine the chemical relationship to morphine, and in this investigation we have already certain facts to guide us. It is known that when thebaine, which is also a morpholine derivative, is treated with hydrochloric acid, a methoxyl group is hydrolysed, and one of two products is formed, according to the conditions of experiment, thebenine being obtained with dilute hydrochloric acid, but morphothebaine with the concentrated acid (Freund, *Ber.*, 1897, 30, 1357; 1899, 32, 168). Knorr has suggested an explanation of the two reactions by means of the following formulæ (*Ber.*, 1899, 32, 746):



It seems likely that chloromorphide or bromomorphide, on treatment with water, behave in a similar manner.

With the object of determining the constitution of isomorphine, work is now proceeding in various directions, and preliminary results are recorded in the following pages.

On treatment of the methiodide with acetic anhydride, only a minute quantity of a nitrogen-free product is obtained, which has the same melting point as the phenanthrene derivative obtained in a similar way from morphine methiodide. This fact should exclude a product analogous in constitution to that given above to thebenine, where the morpholine ring is broken at the nitrogen, for derivatives of this character, as Knorr has shown, readily yield nitrogen-free products on treatment with acetic anhydride. Further, the methohydroxide of isomorphine, obtained by the action of silver sulphate on the iodide and subsequent treatment of the sulphate thus produced by barium hydroxide, acts in a way quite analogous to morphine methohydroxide, which Vongerichten has shown to have a phenol-betaine constitution (*Ber.*, 1897, 30, 355), forming a deliquescent, crystalline hydrate; this, when left in a vacuum, yields a powder which combines on warming with methyl iodide with the opening up of an anhydride ring and the formation of the methiodide of a methyl ether.

$$C_{17}H_{18}O_2\begin{matrix}O\\ \diagdown\\ \diagup\\ N(CH_3)_2\end{matrix} + CH_3I = C_{17}H_{18}O_2\begin{matrix}O\cdot CH_3\\ \diagdown\\ \diagup\\ N(CH_3)_2I\end{matrix}.$$

Such a reaction is also possible with isomorphine, and it therefore does not follow that the latter is a secondary base, because the product obtained by treating its methiodide with silver hydroxide (silver sulphate and barium hydroxide) unites directly with methyl iodide.

The investigation of the iodide produced in this way should throw further light on the constitution of isomorphine, and researches are being prosecuted in this direction.

It seems, however, quite likely that isomorphine is analogous in its constitution to morphothebaine. The results are also interesting as they indicate that a slight change in the morphine molecule may render the morpholine ring unstable, and thus account for the non-narcotic action of such substances as chloromorphide and bromomorphide, in view of the fact that simple synthetical morpholine derivatives like naphthalanmorpholine act physiologically like morphine. The further study of the decomposition products of morphine should offer also a chemical *rationale* for the physiological classification of narcotics like codeine, thebaine, morphine, &c., such as has been attempted by Bradbury and others (see Croonian Lectures, Royal College of Physicians, *British Medical Journal*, or *Lancet*, 1899).

Experimental.

Chloromorphide.

Twenty grams of morphine, previously dried at 120°, are introduced into a wide-mouthed flask connected with a long air condenser. Phosphorus trichloride is then added in sufficient quantity to soak through the solid mass of morphine. After a few moments, a vigorous reaction takes place, and the mixture froths up. The reaction is completed by heating for 3—4 hours on a water-bath. The contents of the flask at the end of this time form a homogeneous, light-brown, pasty mass. This is then disintegrated with alcohol, in which it gradually dissolves, and after a short time chloromorphide hydrochloride separates out if only a small quantity of alcohol is employed. It is advisable, however, to add enough alcohol to keep the hydrochloride in solution when the mixture is slightly warmed. It is then diluted with water, made alkaline with sodium carbonate, and extracted four times with chloroform. The chloroform solution is washed several times with water to free it from alcohol, rapidly dried over calcium chloride, filtered, and the chloroform removed by distillation; the residue consists of white, glistening crystals of chloromorphide suspended in ethyl phosphite. The crystals are collected, washed with alcohol, and being already very nearly pure can be employed for further work without any additional purification. From 12—14 grams of base are generally obtained in this way, and a further quantity can be isolated from the syrupy filtrate by dissolving it in pure dry ether and passing dry hydrogen chloride into this solution. A white precipitate of the hydrochloride of the base is obtained; this deliquesces in the air to a pasty mass, which on further

standing gradually becomes hard, and can be readily purified by recrystallisation.

Chloromorphide is a beautifully crystalline product which melts with decomposition at 190°. It is scarcely soluble in ether, although, when freshly precipitated from a solution of its salts by alkalis, it dissolves readily in this solvent, but separates out again almost immediately in a brilliant, crystalline form. It is easily soluble in chloroform, and in methyl and hot amyl alcohols, but only sparingly so in boiling ethyl alcohol. It is insoluble in benzene, light petroleum, and most other organic solvents.

0·1707 gave 0·4214 CO_2 and 0·0917 H_2O. C = 67·32; H = 5·96.
0·1290 „ 0·3180 CO_2 „ 0·0715 H_2O. C = 67·22; H = 6·15.
0·2830 „ 11·8 c.c. moist nitrogen at 20° and 760 mm. N = 4·77.
0·3702 „ by Carius' method, 0·1731 AgCl. Cl = 11·57.

$C_{17}H_{18}O_2NCl$ requires C = 67·4; H = 5·93; Cl = 11·68; N = 4·61 per cent.

A determination of the specific rotation in methyl alcohol gave the following result:

$$\alpha_D = -2°9', l = 1 \text{ dcm.}, c = 0·573, [\alpha]_D = -375·2°.$$

Chloromorphide Hydrochloride is prepared from the base by grinding it up in a mortar with a slight excess of 10 per cent. hydrochloric acid. A pasty mass is at first formed, but on grinding it is rapidly converted into a snow-white powder, which can be readily filtered off from the mother liquor. Its aqueous solution is unstable, for reasons already described, and it can only be recrystallised from water with considerable loss. It dissolves readily in hot alcohol, and on slowly cooling separates in hard crusts of diamond-like, highly refractive, anhydrous crystals.

0·2456 gave, by Carius' method, 0·1969 AgCl. Cl = 19·84.

$C_{17}H_{18}O_2NCl,HCl$ requires Cl = 20·88 per cent.

Its aqueous solution is very strongly lævorotatory.

$$\alpha_D^{20°} = -5°16', l = 1 \text{ dcm.}, c = 1·67, [\alpha]_D^{20°} = -315·3°.$$

The *hydrobromide* is prepared in the same way as the hydrochloride, and is similar in its properties. Neither in this salt nor in the hydrochloride could the halogen acid combined with the base be determined by direct titration with silver nitrate, as the end reaction was not sharp, probably owing to the ease with which the salt is decomposed. The salt used for analysis was recrystallised from absolute alcohol.

0·3241 gave, by Carius' method, 0·2716 of mixed AgCl and AgBr.

$C_{17}H_{18}O_2NCl,HBr$ requires 0·2793 gram.

The specific rotation of the salt recrystallised from alcohol gave the following result:

$\alpha_D^{19°} = -4°26'$, $l = 1$ dcm., $c = 1{\cdot}65$, $[\alpha]_D^{19°} = -268{\cdot}6°$.

Examination of Mother Liquors from preparation of Chloromorphide.—After extracting the alkaline liquors with chloroform until nothing more went into solution, the aqueous residue always gave a fairly copious precipitate with Mayer's reagent, and as the maximum yield of chloromorphide did not amount to more than 75 per cent. of the theoretical, a certain amount of another alkaloid must be present. The alkaline mother liquors were therefore carefully neutralised with dilute hydrochloric acid, and evaporated to a small bulk. On evaporation, the solution became acid, and more alkali was added from time to time to keep it perfectly neutral. The mixture was evaporated to dryness, and the residue extracted with absolute alcohol in a Soxhlet apparatus to separate the alkaloidal salt from the purely inorganic residue. After distilling off the alcohol, the residue was dissolved in water, the solution boiled with a little animal charcoal to decolorise it, made alkaline with sodium hydrogen carbonate, and extracted forty or fifty times with hot amyl alcohol. The base extracted in this way was removed from its amyl alcoholic solution by dilute hydrochloric acid, and the acid solution evaporated to a small bulk. When sufficiently concentrated, radiating clusters of long, silky needles commenced to separate out, in the form characteristic of morphine hydrochloride, and their identity with this salt was proved by a determination of the water of crystallisation.

0·9322 at 120° lost 0·1322 H_2O. $H_2O = 14{\cdot}1$.

$C_{17}H_{19}O_3N,HCl,3H_2O$ requires $H_2O = 14{\cdot}3$ per cent.

A bye-product therefore appears to be formed, which, on heating with water, is readily reconverted into morphine. This product has not yet been isolated. No trace of isomorphine could be detected.

Acetylchloromorphide, $C_{17}H_{17}O_2NCl{\cdot}CO{\cdot}CH_3$, can be prepared from chloromorphide by means of either acetic anhydride or acetyl chloride, the better result being obtained by the use of the latter. Chloromorphide, mixed with about five times its weight of acetyl chloride, was heated for four or five hours on a water-bath in a reflux apparatus. The base nearly all dissolved. At the end of the reaction, the excess of acetyl chloride was distilled off, the residue dissolved in water, sodium carbonate added, and the base extracted with ether. On distilling off the ether, the acetyl derivative remained behind, and was purified by recrystallising two or three times from absolute alcohol and finally from acetone.

Acetylchloromorphide forms small, white, glistening plates, which soften at 173°, and melt at 174—178°, several recrystallisations being required before a specimen can be obtained melting at the higher temperature.

0·1545 gave 0·3813 CO_2 and 0·0880 H_2O. C = 67·31; H = 6·32.
0·1562 „ 0·3849 CO_2 „ 0·0830 H_2O. C = 67·20; H = 5·90.
0·2338 „ by Carius' method, 0·0923 AgCl. Cl = 9·76.
$C_{19}H_{20}O_3NCl$ requires C = 66·00; H = 5·78; Cl = 10·27 per cent.

Although this substance was repeatedly crystallised, a pure specimen could not be obtained.

From the mother liquors, a very small amount of crystalline substance was obtained melting at 137—145°. The quantity was not sufficient for further investigation.

The *hydrochloride* was made by grinding up the base with 10 per cent. hydrochloric acid. It was recrystallised from water, from which it separated in silky needles, but by this means only 1·2 grams of salt were obtained from 5 grams of the base. As the mother liquors from this product decomposed on concentrating, becoming strongly acid, water was evidently an unsatisfactory solvent for recrystallisation. When administered *per os*, this salt produced no narcotic effects.

Bromomorphide.

Phosphorus tribromide acts on dry morphine with such violence that the mixture spontaneously takes fire. For this reason, the tribromide must be diluted with some inactive solvent to obtain a satisfactory result.

Twenty grams of morphine, previously dried at 120°, are thrown into a solution of 20 grams of phosphorus tribromide in 80 grams of chloroform, and the whole heated for four or five hours on a water-bath in a reflux apparatus. At the end of this time, a yellow, pasty mass is formed underneath the chloroform. This is disintegrated with alcohol, of which a quantity about equal in bulk to the chloroform is added. The whole is stirred round and warmed, until a not quite clear, homogeneous solution is obtained. This is then filtered, and the precipitate, consisting of a little yellow phosphorus mixed with hydrobromide of the base, is washed well with hot water, the washings being added to the filtrate, which is finally mixed with about twice its volume of water. The chloroform then separates out. The whole is then added in small quantities at a time, in a separating funnel, to a solution of excess of sodium carbonate over which a layer of ether stands, and the mixture vigorously shaken after each addition. The base is thus set free from the solution of its hydrobromide, and extracted with the mixture of chloroform and ether. Great care must be taken to prevent the base separating in pasty lumps, for these are not readily soluble in the chloroform-ether mixture; if formed, they must be redissolved in acid, the base regenerated from this, and extracted as just described. Bromomorphide is readily soluble in chloroform, but on concentrating the solution in this solvent, a hard,

porcelain-like mass is obtained, consisting of a mixture of the base with chloroform, from which the chloroform can only be expelled with great difficulty. On the other hand, the base is too slightly soluble in ether for it to be advisable to use this solvent alone. Satisfactory results, however, are obtained by the employment of the ether-chloroform mixture. After extracting four times with a mixture of chloroform and ether, very little of the base remains in the aqueous mother liquors. The chloroform-ether extract is then washed four or five times with water to extract the alcohol, rapidly dried with calcium chloride, filtered, and distilled. The base remains behind as a porcelain-like mass with a certain amount of chloroform adhering. On warming for some time on a water-bath with alcohol and then evaporating, a thick syrup is obtained, which is free from chloroform, and solidifies on standing for a short time to a hard mass, which can be readily powdered in a mortar. After drying the powder thus obtained in a water oven, it is further purified by recrystallisation. About 20 grams of base in this crude form are obtained from 20 grams of morphine.

In order to purify the product, the only convenient solvent available is ether. As, however, it is only slightly soluble in this liquid, it is placed in a Soxhlet apparatus, and extracted for several hours with pure dry ether. It then separates from the ether in hard masses of minute crystals, which are collected, and are quite pure enough for most purposes. A further amount of the base is obtained by concentration of the ethereal mother liquor. For analysis the substance was recrystallised from ether two or three times. After the first ethereal extraction a certain amount of product remains undissolved. This has not yet been further investigated. As a rule, about 45 grams of recrystallised base are obtained from 60 grams of crude product.

Bromomorphide forms a microcrystalline powder of intensely bitter, nauseous taste. It is readily soluble in alcohol or chloroform, but only slightly so in pure dry ether. From benzene or ethyl acetate it separates in a gelatinous form, resembling that obtained from chloroform. It melts at 169—170°.

0·1692 gave 0·3694 CO_2 and 0·0841 H_2O. C = 59·5; H = 5·52.
0·1227 „ 0·2677 CO_2 „ 0·0622 H_2O. C = 59·5; H = 5·63.
0·5030 „ 18·8 c.c. moist nitrogen at 21° and 763 mm. N = 4·27.
0·3620 „ 0·1904 AgBr. Br = 22·38.
$C_{17}H_{18}O_2NBr$ requires C = 58·62; H = 5·17; N = 4·02; Br = 23·00 per cent.

A determination of the specific rotation in methyl alcohol gave the following result:

$$[\alpha]_D = +1°52', l = 1 \text{ dcm.}, c = 2·837, [\alpha]_D^{25°} = +65·9°.$$

Bromomorphide is also obtained when morphine is mixed with four or five times its weight of 45 per cent. hydrobromic acid solution, and the whole heated for 2 or 3 minutes over a free flame, until the mixture begins to darken in colour. The product is then made alkaline with sodium carbonate, and the base extracted with an ether-chloroform mixture. A little unchanged morphine remains undissolved. For preparing large quantities of bromomorphide, the phosphorus tribromide method is the more convenient.

The salts of bromomorphide are much more stable than those of the corresponding chloro-compound, and for this reason can be recrystallised from water with very little loss. They are made by grinding up the base with a slight excess of acid. The *hydrochloride* crystallises from water in glistening needles containing $1H_2O$.

0·4545, at 115°, lost 0·0188 H_2O. $H_2O = 4·14$.

$C_{17}H_{18}O_2NBr,HCl,H_2O$ requires $H_2O = 4·47$ per cent.

0·3646 air-dried substance gave 0·3022 mixed AgCl and AgBr. AgCl + AgBr calc. = 0·3 gram.

For the determination of the specific rotation, the anhydrous salt obtained by recrystallisation from alcohol was employed.

$$\alpha_D = +1°17'\ ;\ l = 1\ \text{dcm.}\ ;\ c = 3·157\ ;\ [\alpha]_D^{27°} = +41·1°.$$

The *hydrobromide* is very similar in appearance to the hydrochloride.

0·7492, at 120°, lost 0·0355 H_2O.* $H_2O = 4·73$.

0·2720 air-dried substance gave 0·2242 AgBr. Br = 35·07.

$C_{17}H_{18}O_2NBr,HBr,H_2O$ requires $H_2O = 4·03$; Br = 35·77 per cent.

For the determination of the specific rotation a specimen recrystallised from alcohol was employed:

$$\alpha_D = +1°0'\ ;\ l = 1\ \text{dcm.}\ ;\ c = 2·53\ ;\ [\alpha]_D^{25°} = +39·5.$$

Deoxymorphine.

Chloromorphide was suspended in about five times its weight of concentrated hydrochloric acid, excess of granulated tin added to the mixture, and the whole heated for 2 or 3 hours on a water-bath. A thick syrup separated out after a time. The liquid was poured off from the undissolved tin, which was then washed several times with hot water to dissolve out all the separated syrup. After filtration, the liquid was saturated with hydrogen sulphide whilst still warm, then corked up, and allowed to stand for some time. The precipitated stannous sulphide is subsequently filtered off and washed with hot water, the washings being added to the filtrate, which is then concen-

* Slight decomposition takes place at 120°, the substance becoming somewhat coloured.

trated over a free flame, under diminished pressure. If not concentrated too far, crystals of the new hydrochloride will separate out, and these, after filtering off and recrystallising once or twice from hot water, are quite pure. If, however, the new hydrochloride separates as an oil, it is advisable to neutralise carefully the strongly acid liquid with caustic soda and evaporate to dryness in a vacuum. The product thus obtained is then ground up to a fine powder, and extracted with absolute alcohol to separate the hydrochloride of the base from the inorganic salts with which it is mixed. On evaporation of the alcoholic extract, a syrup is obtained, which partly solidifies on mixing with water. The solid part can then be collected and recrystallised from water. Owing to the large amount of uncrystallisable matter, the yield of this hydrochloride was very small, and various attempts were made to increase the amount, but without success. As the product could not be obtained in large quantities, it was not subjected to a detailed investigation.

The hydrochloride separates from water in glistening needles containing $1\frac{1}{2}H_2O$. The base is soluble in ether, but has not yet been investigated.

0·8050, at 120°, lost 0·0665 H_2O. $H_2O = 8·25$.
0·1196 gave 0·2707 CO_2 and 0·0748 H_2O. $C = 61·66$; $H = 6·94$.
0·3592 „ 12·8 c.c. moist nitrogen at 19° and 755 mm. $N = 4·06$.
0·3135* „ 0·1333 AgCl. $Cl = 10·52$.
$C_{17}H_{19}O_2N,HCl,1\frac{1}{2}H_2O$ requires $C = 61·35$; $H = 6·91$; $N = 4·21$; $Cl = 10·7$; $H_2O = 8·12$ per cent.

The specific rotation was determined with a specimen recrystallised from water:

$$\alpha_D = +3°19'; \; l = 1 \text{ dcm.}; \; c = 2·363; \; [\alpha]_D^{27°} = +140·3°.$$

Isomorphine.

Isomorphine is most conveniently prepared from bromomorphide. For this purpose, 15 grams of bromomorphide are heated in a reflux apparatus with 150 c.c. of water, care being taken that the suspended base is not superheated, the flask, on this account, being repeatedly shaken. After about 1 hour the whole of the bromomorphide disappears, and a clear, light brown liquid is formed, which can be partly decolorised by boiling with animal charcoal. After filtering from the animal charcoal, the liquid is concentrated to a syrupy consistence. On stirring, the syrup partly solidifies to a thick, crystalline paste. The crystals are then separated from the mother liquors, washed

* This analysis was done by Carius' method, in order to be sure that there was no chlorine in the substance other than that in the acid.

with a little alcohol, and spread on a porous plate. They are already nearly white; owing to their extreme solubility in water, purification is best effected by dissolving them in a large quantity of hot alcohol, and concentrating the solution until the hydrobromide separates out as a crystalline powder.

The *hydrobromide* crystallises from water, with $1H_2O$, in hard, stumpy prisms.

0·7078, at 110—120°, lost 0·0360 H_2O. $H_2O = 5·08$.
$C_{17}H_{19}O_3N,HBr,H_2O$ requires $H_2O = 4·69$ per cent.

It separates from alcohol as a granular, crystalline powder, without water of crystallisation.

0·2161 gave 0·4466 CO_2 and 0·1058 H_2O. C = 56·36; H = 5·40.
0·1688 ,, 0·3470 CO_2 ,, 0·0840 H_2O. C = 56·06; H = 5·50.
0·2817 ,, 0·1433 AgBr. Br = 21·64.
$C_{17}H_{19}O_3N,HBr$ requires C = 55·75; H = 5·46; Br = 21·85 per cent.

A determination of the specific rotation gave the following result:

$$\alpha_D = -3°10'; \; l = 1 \text{ dcm.}; \; c = 2·49; \; [\alpha]_D^{15°} = -127·2°.$$

The corresponding salt of morphine crystallises with $2H_2O$, and when recrystallised from alcohol in the anhydrous form gave for the specific rotation the following result:

$$\alpha_D = -5°; \; l = 2 \text{ dcm.}; \; c = 2·49; \; [\alpha]_D^{15°} = -100·4°.$$

In order to obtain salts other than the hydrobromide, the solution of the latter, obtained by decomposition of bromomorphide, is concentrated, made alkaline with sodium carbonate, and extracted five or six times with hot amyl alcohol. To prepare the hydrochloride, the amyl alcoholic solution is extracted with dilute hydrochloric acid, and the acid solution evaporated to a syrup and left to crystallise.

The *hydrochloride* is excessively soluble in water, from which it separates in beautiful, transparent, anhydrous, regular octahedra. The specimen analysed was recrystallised from a large quantity of absolute alcohol, in which it is only slightly soluble.

0·2913 required 9·2 c.c. $N/10$ $AgNO_3$. Cl = 11·21.
$C_{17}H_{19}O_3N,HCl$ requires Cl = 11·04 per cent.

A determination of the specific rotation gave the following result:

$$\alpha_D = -7°9', \; l = 1 \text{ dcm.}, \; c = 4·76, \; [\alpha]_D^{20°} = -150°.$$

The corresponding morphine salt crystallises from water in masses of long, silky, radiating needles containing $3H_2O$, and is soluble in about 20 times its weight of water. For purposes of comparison, a

specimen, free from water of crystallisation, was prepared by recrystallising from alcohol, and gave the following result :

$$\alpha_D = -2°30', l = 1 \text{ dcm.}, c = 2·240, [\alpha]_D^{25°} = -111·5°.$$

The *sulphate* was prepared by treating the hydrochloride with a solution of silver sulphate and evaporating the filtrate very nearly to dryness. It is excessively soluble in water, but insoluble in alcohol, and could not therefore be recrystallised. For this reason, its properties were not accurately determined, but it differs very markedly from the neutral sulphate of morphine.

Isomorphine was originally prepared by treating a concentrated solution of the hydrobromide with aqueous ammonia in the presence of ether ; the freshly precipitated base is dissolved by the ether, from which, however, it rapidly separates again in a beautiful, crystalline form. Only a portion of the base could be obtained in this way, even after 15 or 20 extractions with ether. The rest remained in the alkaline liquid, and on evaporating the latter to dryness in a vacuum, a mixture of the hydrobromide with ammonium bromide was obtained. The base is best obtained, however, by decomposing the hydrochloride by sodium methoxide in methyl alcohol. Sodium chloride is precipitated, and after filtration the nearly pure base is obtained from the mother liquor.

Isomorphine is free from any bitter taste. It dissolves in large quantities of ethyl alcohol, is readily soluble in methyl alcohol, but not very readily so in most other organic reagents, and can best be recrystallised from a mixture of methyl alcohol and ethyl acetate, from which it separates in the form of small, white, glistening needles melting at 246—248°. It is also soluble in, and can be recrystallised from, hot water.

0·1638 gave 0·4320 CO_2 and 0·1004 H_2O. C = 71·92 ; H = 6·81.
0·2690 „ 11·8 c.c. moist nitrogen at 24° and 757 mm. N = 4·90.
$C_{17}H_{19}O_3N$ requires C = 71·6 ; H = 6·66 ; N = 4·91 per cent.

A determination of the specific rotation was made with a solution of the base in methyl alcohol, and gave the following result :

$$\alpha_D = -3°17', l = 1 \text{ dcm.}, c = 2·01, [\alpha]_D^{25°} = -164·3°.$$

Morphine* is similar to isomorphine in many respects, and melts at 254°. A specimen, recrystallised from methyl alcohol, from which it separates in beautiful groups of radiating crystals, gave the following

* It does not seem to be generally known that morphine can be readily recrystallised from various solvents, especially methyl alcohol, in which it is quite readily soluble.

numbers when its specific rotation in methyl alcoholic solution was determined.

$$\alpha_D = -3°0', l = 1 \text{ dcm.}, c = 2·292, [\alpha]_D^{23°} = -130·9°.$$

The colour reactions of isomorphine are similar to those of morphine.

Isomorphine Methiodide.—4·2 grams of isomorphine and 5 grams of methyl iodide were dissolved in 150 c.c. of methyl alcohol and the mixture boiled on a water-bath. After about 20 minutes, the methiodide commenced to separate. The boiling was continued for 1 hour, at the end of which time the crystals of the methiodide were filtered off. A further small quantity was obtained from the mother liquors. After drying at 80°, the substance was found to melt with some decomposition at 276°. It is soluble in hot water, from which it separates on cooling in the form of white, glistening needles. It dissolves readily in 25 per cent. caustic soda solution.

0·3980 required 9·35 c.c. $N/10$ $AgNO_3$ solution. I = 30·0.

$C_{17}H_{19}O_3N,CH_3I$ requires I = 30·6 per cent.

A determination of the specific rotation in water gave the following results:

$$\alpha_D = -1°38', l = 1 \text{ dcm.}, c = 1·696, [\alpha]_D^{23°} = -91·5°.$$

Morphine methiodide melts at nearly the same temperature as the isomorphine derivative. A determination of its specific rotation in water gave the following result:

$$\alpha_D = -0°51', l = 1 \text{ dcm.}, c = 1·162, [\alpha]_D^{25°} = -72·9°.$$

Action of Acetic Anhydride on Isomorphine Methiodide.—Four grams of isomorphine methiodide were suspended in 40 grams of acetic anhydride, to this was added $\frac{1}{2}$ gram fused sodium acetate, and the whole boiled on a sand-bath until solution was effected, when 1·6 grams of silver acetate (1 mol.) were introduced. Immediate precipitation of silver iodide occurred, and the mixture was boiled in an oil-bath for 6 hours. Silver iodide was then filtered off, and the filtrate heated in a sealed tube for 3 hours at 180°. The acetic anhydride was then distilled off at 170° in an oil-bath, and the concentrated, light brown solution poured into twice its volume of water. A small quantity of a brown oil separated, which quickly solidified, and was collected, powdered, and dried. The crude substance only amounted to 0·3 gram. This was dissolved in glacial acetic acid, the solution boiled with animal charcoal, and filtered. On cooling, the filtrate deposited small, glistening needles, which were collected and found to melt at 154—155°. They were then recrystallised from a large quantity of dry ether, from which they separated in small, white needles melting at 158—158·5°. O. Fischer and Vongerichten obtained an acetyl di-

hydroxyphenanthrene from morphine methiodide which melted at 159° (*Ber.*, 1886, **19**, 792). The filtrate from the solid product, which contains the main product of the action of acetic anhydride and silver acetate on morphine methiodide, when made alkaline, deposits a base which has not yet been investigated.

Further reactions of Isomorphine Methiodide.—2·1 grams of isomorphine methiodide were dissolved in hot water, and to this an aqueous solution of 0·78 gram of silver sulphate was added. The precipitated silver iodide was filtered off, and to the filtrate an aqueous solution of 0·8 gram of crystallised barium hydroxide was added, and the whole boiled. Carbon dioxide was passed through for a short time to precipitate the very slight excess of baryta. After filtration from the precipitated barium sulphate, the strongly alkaline solution was evaporated to a syrup, which, when placed in a vacuum, deposited a mass of fern-like crystals. On further evaporation in a vacuum, the crystals dissolved, and a syrup was obtained which, on standing overnight, became a hard, solid mass. This, when powdered and dissolved in methyl alcohol, gave a strongly alkaline solution. Excess of methyl iodide was added, and the mixture allowed to stand for 2 days. At the end of this time, it was still strongly alkaline, and did not become neutral until boiled on a water-bath for 1 hour. The methyl alcohol, with excess of methyl iodide, was evaporated off, leaving a syrup which was dissolved in water, and the solution boiled with animal charcoal, filtered, evaporated on a water-bath to a syrup, and placed in a vacuum over sulphuric acid. The resulting varnish gradually became quite hard, and could be powdered; it was deliquescent, and almost insoluble in ethyl alcohol, but readily soluble in methyl alcohol or cold water. It did not agree in any of its properties with codeine methiodide.

0·3908 required 8·7 c.c. $N/10$ $AgNO_3$. I = 28·2.

$C_{17}H_{18}(OCH_3)O_2N,CH_3I$ requires I = 28·8 per cent.

A determination of the specific rotation in water gave the following result:

$$\alpha = -2°0',\ l = 1 \text{ dcm.},\ c = 2·074,\ [\alpha]_D^{25} = -96·4°.$$

Preliminary experiments have been made for the preparation of the acetyl compound, and the results will be communicated in a later paper.

Addendum.—Since the communication of the above paper to the Society, Pschorr and Sumuleanu have published their synthesis of morphol (*Ber.*, 1900, **33**, 1810), and confirmed the formula assigned to this substance by Vongerichten.

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